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A measure of the extent of delay in release of active pharmaceutical ingredient of the experimental formulations was the time to reach maximum concentration (T_{max}) values observed for anagrelide. The T_{max} values were approximately 2 hours later than that observed for Agrylin®, demonstrating about a 2.6-fold delay in time to reach C_{max} for the three extended release formulations compared with the immediate-release Agrylin®. Furthermore, the length of time at which the anagrelide plasma concentration remained above $\frac{1}{2}C_{max}$ ($T_{width \frac{1}{2}C_{max}}$) was approximately two- to three-fold greater for the extended release formulations than the immediate release formulation, demonstrating good extended release characteristics.

No serious adverse events were reported. One subject discontinued due to an adverse event (head cold) considered not related to study drug. There were a total of 46 adverse events (AEs) experienced by eleven (11) subjects. The most frequently reported events (>5%), included asthenia, headache, somnolence, and dizziness, and were not unexpected. These events have been reported frequently by the target patient population at large receiving Agrylin® for the treatment of thrombocytopenia secondary to all myeloproliferative disorders. Treatment emergent AEs are summarized in Table 9.

TABLE 9

Treatment Emergent AEs		
Preferred Term (Costart)	Count	% (n = 12)
Asthenia	12	26.1
Headache	9	19.6
Somnolence	6	13.0
Dizziness	5	10.9
Tachycardia	2	4.3
Infection	2	4.3
Nausea	2	4.3
Vomit	2	4.3
Pain Abd	1	2.2
Palpitations	1	2.2
Pain	1	2.2
Hem	1	2.2
Voice alteration	1	2.2
Thirst	1	2.2
Total	46	100.0

The data would indicate that adverse events (AEs) observed in subjects following dosage with the extended release formulation were not as prevalent as AEs observed following the immediate release formulation (Agrylin®). More than 50% of the reported AEs were observed following Agrylin® administration. The number of adverse events following administration of the new extended release formulations were 8/46 (17%) for Formulation 1, 9/46 (20%) for Formulation 2, and 4/46 (9%) for Formulation 3 compared to 25/46 (54%) for the marketed Agrylin®. The incidence of subjects reporting adverse events for the new extended-release formulations (4/12 (33%), 6/12 (50%), and 2/12 (17%) for Formulations 1, 2, and 3, respectively) also were substantially lower than the incidence observed in the Agrylin® group (10/12 (83%)). The number and percentage of subjects reporting adverse events are presented in Table 10.

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TABLE 10

Treatment Emergent Adverse Events per Treatment Group				
Drug Treatment	Preferred Term (Costart)	No. Subjects Reporting	% Subjects Reporting	No. AEs Reported
Formulation 1 (n = 12)	Asthenia	3	25.0	3
	Nausea	1	8.3	1
	Pain	1	8.3	1
	Somnolence	1	8.3	1
	Thirst	1	8.3	1
	Vomit	1	8.3	1
Formulation 2 (n = 12)	Asthenia	3	25.0	3
	Dizziness	2	16.7	2
	Headache	2	16.7	2
	Somnolence	1	8.3	1
Formulation 3 (n = 11)	Hem	1	8.3	1
	Asthenia	1	9.3	1
	Headache	1	9.3	1
	Infect	1	9.3	1
	Voice alteration	1	9.3	1
Agrylin® (n = 12)	Headache	6	50.0	6
	Asthenia	5	41.7	5
	Somnolence	3	25.0	4
	Dizziness	3	25.0	3
	Tachycardia	2	16.7	2
	Nausea	1	8.3	1
	Pain Abdominal	1	8.3	1
	Infect	1	8.3	1
	Vomit	1	8.3	1
	Palpitations	1	8.3	1
Total (n = 12)				46

With respect to clinical laboratory and physical examination findings, statistically significant ($p < 0.01$) increases in pulse compared with baseline were observed with Agrylin® at 2, 4, and 24 hours post dose. Significant increases were observed at 24 hours post dose for Formulations 1 and 3. Only Agrylin® showed a statistically significant changed from baseline for blood pressure (i.e. at 24 hours post dose for diastolic blood pressure).

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

What is claimed is:

1. A pharmaceutical composition, comprising:

- guanfacine;
- hydroxypropyl methylcellulose;
- ammonip methacrylate copolymer;
- microcrystalline cellulose;
- a methacrylic acid copolymer;
- glyceryl behenate;
- fumaric acid;
- lactose monohydrate;
- povidone; and
- crospovidone granulated blend.

2. A pharmaceutical composition, comprising:

- guanfacine hydrochloride;
- hydroxypropyl methylcellulose;
- ammonio methacrylate copolymer;
- microcrystalline cellulose;
- a methacrylic acid polymer;
- glyceryl behenate;